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Idiopathic Scoliosis

Number: 0398

Policy

I. Aetna considers surface electrical muscle stimulators (direct or alternating current, not high-voltage galvanic current) experimental and investigational for the management of idiopathic scoliosis because there is inadequate evidence of its effectiveness and safety in the peer-reviewed published medical literature.

II. Aetna considers surgery (e.g., spinal fusion with instrumentation and bone grafting) for the treatment of idiopathic scoliosis medically necessary for any of the following conditions:

A. An increasing curve (greater than 40 degrees) in a growing child; *or*
B. Scoliosis related pain that is refractory to conservative treatments; *or*
C. Severe deformity (curve greater than 50 degrees) with trunk asymmetry in children and adolescents; *or*
D. Thoracic lordosis that can not be treated conservatively.

Policy History

Last Review 06/13/2017
Effective: 05/04/2000
Next Review: 04/12/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Aetna considers idiopathic scoliosis surgery experimental and investigational when these criteria are not met.

III. Aetna considers growing rods technique medically necessary in the treatment of idiopathic scoliosis for persons who meet criteria for surgery above. Please note this include the MAGEC System; but does not apply to other expandable magnetic growing rods (e.g., Phenix Growing Rod device) which are considered investigational and experimental.

IV. Scoliosis braces and casts

A. Aetna considers the following types of braces and casts medically necessary DME for the treatment of scoliosis:

1. Boston scoliosis brace
2. Charleston scoliosis brace
3. Milwaukee scoliosis brace
4. Providence brace
5. Rigo-Cheneau brace
6. Risser jacket
7. Standard thoracolumbrosacral orthosis orthosis (TLSO).

B. Aetna considers the following types of scoliosis braces experimental and investigational because their effectiveness has not been established:

1. Copes scoliosis brace
2. Rosenberger brace
3. SpineCor Dynamic Corrective Brace.

V. Aetna considers spinal unloading devices (e.g., LTX 3000, Orthotrac) experimental and investigational for treatment of scoliosis because their effectiveness has not been established. See also **CPB 0569 - Lumbar Traction Devices (../500_599/0569.html)**.

VI. Aetna considers vertebral body stapling and vertebral body tethering experimental and investigational for the treatment of scoliosis because its effectiveness has not been established.

VII. Aetna considers resistive exercises (including the Schroth method) experimental and investigational for the treatment of scoliosis because their effectiveness for this indication has not been established.

VIII. Aetna considers spinal manipulation experimental and investigational for the treatment of adult scoliosis because its effectiveness for this indication has not been established. See also **CPB 0107 - Chiropractic Services (../100_199/0107.html)**.

IX. Aetna considers whole body vibration experimental and investigational for the treatment of scoliosis because its effectiveness has not been established.

X. Aetna considers ScoliScore and other genetic testing (e.g., the CHD7 gene, estrogen receptor beta (ESR2) rs1256120 single nucleotide polymorphism (SNP) testing, insulin-like growth factor 1 (IGF1) gene rs5742612 SNP testing, the matrilin-1 gene (MATN1), melatonin receptor 1B gene (MTNR1B) rs4753426 and rs10830963 polymorphism testing, and the transforming growth factor beta 1 (TGFB1) gene; not an all-inclusive list) experimental and investigational for predicting progression of adolescent idiopathic scoliosis because their effectiveness has not been established.

XI. Aetna considers the following interventions for the treatment of scoliosis experimental and investigational because their effectiveness has not been established:

- Manual therapy
- The CLEAR protocol
- The inversion table
- The magnetically controlled growing rods (e.g., the Phenix growing rod) (except for the MAGEC System)
- Sacroiliac fusion.

Note: Some plans exclude coverage of DME. Please check benefit plan descriptions for details.

Background

Scoliosis may be classified as functional or structural. Functional scoliosis may be transient or fairly persistent, but is not associated with any structural alterations. Structural scoliosis involves a fixed lateral curve with rotation, and is associated with many conditions including neuropathic diseases/disorders such as cerebral palsy, poliomyelitis, and muscular dystrophy; congenital causes such as failure of formation or segmentation, and myelomeningocele; traumatic causes such as fracture or dislocation (non-paralytic) and post-radiation; soft tissue contractures such as post-empyema and burns; osteochondrodystrophies such as achondroplasia and spondyloepiphyseal dysplasia; tumor; and rheumatoid disease. However, the most common type of structural scoliosis is idiopathic scoliosis. Although idiopathic scoliosis is thought to have a genetic predisposition, its exact cause is still unknown.

Idiopathic scoliosis can be further divided into 3 categories: (i) infantile (0 to 3 years of age), (ii) juvenile (3 to 9 years of age), and (iii) adolescent (10 years of

age to maturity). Idiopathic scoliosis most frequently affects young girls. The spinal curvature that persists after skeletal maturity is termed adult scoliosis.

The traditional treatment for adolescent idiopathic scoliosis is the use of a supportive brace, (e.g., the Milwaukee brace, the Boston brace). Torso exercises to increase muscle strength have been used in conjunction with braces, but there is inadequate evidence to support this. Since bracing is restrictive and must be worn 23 hours a day for up to several years, non-compliance has been estimated to be 20 to 50 % (Moe and Kettelson, 1970). Additionally, this method is associated with side effects such as anxiety, depression, and sleep disturbance.

Another non-invasive method to straighten abnormal lateral curvature is surface electrical muscle stimulation. This has been shown not to be effective and is no longer considered standard of care (O'Donnell, et al, 1988). In this approach, muscles on one side of the spine are stimulated electrically (direct or alternating current, not high-voltage galvanic current) to contract and pull the vertebrae into a more normal position. Surface electrical muscle stimulation is usually applied for 8 to 10 hours during sleep. Treatment is terminated when patients reach skeletal maturity and structural stability. It is postulated that electro-muscular stimulation in the scoliotics may produce changes in muscle structure resulting in more fatigue-resistant muscles which increase the ability for postural stabilizing muscle activity in the spine (Grimby et al, 1985). Advantages of surface electrical muscle stimulation include freedom from bracing, the need for only part-time therapy, and an improvement of self-image in the affected adolescents. In severe cases, spinal fusion with instrumentation is effective in halting progression of the curve(s).

Surface electrical muscle stimulation has not been shown by well controlled studies to be effective in reversing or arresting progression of spinal curvatures in adolescents with idiopathic scoliosis. Brown et al (1984) reported the findings of a multi-center study on the use of night-time lateral electrical surface stimulation (LESS) for the treatment of juvenile or adolescent idiopathic scoliotics (484 girls and 64 boys, mean ages of 12.8 and 13.9 years, respectively). Only individuals with rapidly progressing scoliosis and at least 1 year of growth remaining were selected for this trial. The mean treatment time was 12 months, and the longest follow-up was 51 months. During the initial 6 months of therapy, a pre-treatment curvature progression rate of 1 degree/month was reversed to a reduction rate of 0.5 degree/month. Overall, 395 (72 %) patients had either reduced or stabilized their scoliosis. Seventy-one (13 %) patients had experienced temporary progression with subsequent stabilization and treatment continuation, while 82 (15 %) patients dropped out because of progression of their conditions. The major problem with LESS was skin irritation. The authors concluded that LESS treatment is a viable alternative to bracing for patients with idiopathic scoliosis.

Dutro and Keene (1985) performed a literature review on surface electrical muscle stimulation in the treatment of progressive adolescent idiopathic scoliosis. Patient selection criteria for studies reviewed were as follows: (i) Cobb angle of 25 to 45 degrees as indicated by radiographic studies, (ii) documented history of progression, (iii) minimum of 50 % correction on forced lateral bending, and (iv) minimum of 1 year of bone growth remaining. The authors concluded that electro-muscular stimulation is equally effective as bracing in treating progressive adolescent idiopathic scoliosis -- progression was arrested in 60 to 84 % of treated curves. The authors stated that, for juvenile scoliosis, if treatment begins early enough and progression is not

too severe, a curve cannot only be arrested, but reversed. Surface electro-muscular stimulation can also be employed to halt progression while patients await surgery.

A prospective study by the Scoliosis Research Society (Nachemson & Peterson, 1995) found electrical stimulation to be less effective than bracing and no more effective than observation in idiopathic scoliosis. In this study, 286 girls who had adolescent idiopathic scoliosis, a thoracic or thoracolumbar curve of 25 to 35 degrees, and a mean age of 12 years and seven months (range, 10 to 15 years) were followed to determine the effect of treatment with observation only (129 patients), an underarm plastic brace (111 patients), and nighttime surface electrical stimulation (46 patients). Thirty-nine patients were lost to follow-up, leaving 247 (86 percent) who were followed until maturity or who were dropped from the study because of failure of the assigned treatment. The endpoint of failure of treatment was defined as an increase in the curve of at least 6 degrees, from the time of the first x-fay, on two consecutive x-rays. As determined with use of this endpoint, treatment with a brace failed in seventeen of the 111 patients; observation only, in 58 of the 129 patients; and electrical stimulation, in 22 of the 46 patients. According to survivorship analysis, treatment with a brace was associated with a success rate of 74 percent (95 percent confidence interval, 52 to 84) at four years; observation only, with a success rate of 34 percent (95 percent confidence interval, 16 to 49); and electrical stimulation, with a success rate of 33 percent (95 percent confidence interval, 12 to 60). The 39 patients who were lost to follow-up were included in the survivorship analysis for the time period that they were in the study. Treatment with a brace was successful ($p < 0.0001$) in preventing six degrees of increase or more until the patients were 16 years old. The investigators noted that, even a worst-case analysis, in which the 23 patients who were

dropped from the study after management with a brace were considered to have failed treatment, showed that the brace prevented progression and that this effect was significant ($p = 0.0005$). The investigators reported that there was no difference in the degree of increase in the curve between the patients who were managed with observation only and those who were managed with electrical stimulation.

The peer-reviewed medical literature suggest that surgery is indicated for growing children whose curve has exceeded 40 degrees; for individuals of any age whose curve is greater than 50 degrees; individuals with scoliosis-related pain that is refractory to conservative treatments; and patients with thoracic lordosis that can't be treated conservatively.

Braces are a primary treatment for idiopathic scoliosis. Standard scoliosis braces include the Milwaukee brace and the Boston brace.

Unlike other commonly used scoliosis braces, such as the Boston brace and the Milwaukee brace, the Charleston brace is worn only at night. Clinical studies have been published that have shown that the Charleston brace compares favorably to the traditional Boston and Milwaukee TLSO braces (Trivedi et al, 2001; Gepstein et al, 2002; Howard et al, 1998). The Charleston brace is especially useful for children with scoliosis who are not compliant with a traditional Boston or Milwaukee TLSO brace or who do not respond well to TLSO braces (Roach, 2002).

Unlike other commonly used scoliosis braces, such as the Boston brace, Wilmington brace (custom fit TLSO) and the Milwaukee brace (CTLSO), the Charleston and the Providence braces are worn only at night. Clinical studies have shown that for curves under 35 degrees the Charleston brace compares favorably to the traditional

Boston, custom fit TLSOs, and Milwaukee (CTLSO) braces. (Trivedi et al, 2001; Gepstein et al, 2002; Howard et al, 1998). The Charleston brace may be useful for children with scoliosis who are not compliant with a traditional Boston or Milwaukee TLSO brace or who do not respond well to TLSO braces (Roach, 2002).

The Providence Scoliosis System is similar to the Charleston brace but has the added advantage of derotation forces and likewise is designed to be worn only at night (d'Amato, et al., 2001). The Providence Scoliosis System includes pressure sensors to ascertain if sufficient pressure is being administered. Recent work by Janiski et al showed the Providence brace to be more effective for curves less than 35 degrees as compared to standard TLSO which may be because of better compliance. A report by d'Amato et al (2001) of their experience with the first consecutive 102 patients with adolescent idiopathic scoliosis treated with the Providence brace who were followed for 2 years after completing treatment. Yrjonen et al (2006) evaluated the results of treatment of adolescent idiopathic scoliosis (AIS) with the Providence night-time brace at 1.8 years after discontinuation of bracing. A total of 36 female patients with an average Cobb angle of 28.4 degrees and an apex below T-10 were studied prospectively. For comparisons, 36 matched patients treated with the Boston full-time brace were studied retrospectively. With the Providence night brace an average of 92 % for brace correction of the primary curve was achieved and during follow-up progression of the curve greater than 5 degrees occurred in 27 % of the patients. In the control group of the Boston full-time brace patients, brace correction was 50 % and the progression of the major curve occurred in 22 % of the patients. The authors concluded that the Providence night brace may be recommended for the treatment of AIS with curves less than 35 degrees in lumbar and thoracolumbar cases.

The Copes Scoliosis Brace is a custom-fitted polypropene support structure that utilizes air to attain spinal curvature correction. This is achieved through the use of strategically placed pneumatic force vector pads that are adjusted every 4 to 6 weeks during treatment. The brace is generally used for 12 to 36 months in conjunction with hydrotherapy, regular muscle strengthening exercises, as well as chiropractic treatments such as osseous manipulation and muscle stimulation therapy. There is no scientific evidence that the Copes Scoliosis Brace is effective in treating scoliosis. Additionally, there are no published data concerning the long-term effectiveness of this device, the rate of recurrence of scoliosis after patients stop wearing the brace or the number of patients who eventually have to undergo surgical intervention. Furthermore, the Copes Scoliosis Brace is used in conjunction with hydrotherapy, regular muscle strengthening exercises and chiropractic treatments. Thus, it is unclear what role the brace actually plays in the improvement, if any, of the condition. Similar to the Copes system is the “Clear method “of treating scoliosis. Likewise there is no data to support the Clear method .

There is a lack of scientific evidence in the peer-reviewed published medical literature to support the effectiveness of the SpineCor Scoliosis System in treating idiopathic scoliosis, including insufficient data on its long-term effectiveness and a lack of studies directly comparing the dynamic corrective brace with rigid bracing systems.

In a prospective, observational study, Couillard and colleages (2007) assessed the effectiveness of the Dynamic SpineCor brace for adolescent idiopathic scoliosis in accordance with the standardized criteria proposed by the Scoliosis Research Society Committee on bracing and non-operative management. From 1993 to 2006, 493 patients were treated using the SpineCor

brace. A total of 249 patients met the criteria for inclusion, and 79 patients were still actively being treated. Overall, 170 patients have a definitive outcome. All girls were pre-menarchal or less than 1 year post-menarchal. Assessment of brace effectiveness included (i) % of patients who have 5 degrees or less curve progression, and % of patients who have 6 degrees or more progression; (ii) % of patients who have been recommended/undergone surgery before skeletal maturity; (iii) % of patients with curves exceeding 45 degrees at maturity (end of treatment); and (iv) 2-year follow-up beyond maturity to determine the % of patients who subsequently underwent surgery. Successful treatment (correction, greater than 5 degrees, or stabilization, +/- 5 degrees) was achieved in 101 (59.4 %) of the 170 patients from the time of the fitting of the SpineCor brace to the point in which it was discontinued. Thirty-nine immature patients (22.9 %) required surgical fusion while receiving treatment. Two (1.2 %) of 170 patients had curves exceeding 45 degrees at maturity. One mature patient (2.1 %) needed surgery within 2 years of follow-up beyond skeletal maturity. The authors concluded that the SpineCor brace is effective for the treatment of adolescent idiopathic scoliosis. Moreover, positive outcomes are maintained after 2 years because 45 (95.7 %) of 47 patients stabilized or corrected their end of bracing Cobb angle up to 2 years after bracing. The results of this observational study are promising; however the findings need to be validated by future well-designed studies.

Wong and colleagues (2007) stated that the conventional rigid spinal orthosis and the flexible spinal orthosis, SpineCor, have different treatment principles in the management of AIS. These may influence the patients' gait pattern and clinical outcome. In this study, gait analysis on patients with AIS undergoing these 2 orthotic interventions were conducted. The patients' lower limb kinematic and kinetic data during level

walking were collected using a motion analysis system and 2 force platforms in 4-test conditions: pre-intervention, having used the orthosis for 1 month and 1 year (in and out of the orthosis). A total of 21 subjects were randomly assigned to the rigid spinal orthosis group (10 subjects) and the SpineCor group (11 subjects). Neither group showed gait asymmetry when comparing the convex and concave sides in the 4-test conditions. However, significant reduction in the range of motion of the pelvis and hip joints in the coronal plane were found. Although patients with AIS undergoing these 2 orthotic interventions showed significant changes in walking pattern within the study period, their long-term effect on gait and function requires further investigation through long-term prospective studies.

The Rosenberger brace is a low-profile, custom-molded thoracolumbosacral orthosis (TLSO) that includes design changes from other TLSOs that are intended to improve compliance and, therefore, outcomes. The Rosenberger low profile orthoses is intended to offer better appearance than the Milwaukee orthosis with its neck ring (Gavin et al, 1986). While the Rosenberger brace was developed in the 1980's, the effectiveness of the brace had never been evaluated in the literature prior to 2004 (Gavin et al, 1986; Grabowski and Gelb, 2005). At that time, Spoonamore et al (2004) assessed the effectiveness of the Rosenberger brace in preventing curve progression in adolescent idiopathic scoliosis (n = 71). The investigators found the brace to have an overall failure rate similar to that of untreated cases from published natural history studies, although subgroups of patients had lower failure rates. These findings suggested the need for further refinement of the indications for the Rosenberger brace.

The Cheneau brace is a thermo-plastic scoliosis brace modeled on a hyper-corrected positive plaster cast of the patient. This is a 3-dimensional (3-D) correctional brace that has significant pressure and expansion areas built into the brace, which provides correction in all 3 anatomical planes. It follows the general correction principle as was written by Dubousset -- detorsion and sagittal plane normalization, which would effect correction of the coronal and transversal planes, resulting in some elongation of the spine, without any significant distraction force. The Rigo System Cheneau (RSC) brace is a scoliosis brace that is based on the original theories of Dr. Cheneau, however Dr. Rigo furthered the designs by combining his new scoliosis classification types, to design the RSC brace also known as El corse de RSC. The brace is manufactured with an Ortholutions CAD CAM technique.

Rigo et al (2002) reported a retrospective series that included 105 idiopathic scoliotic patients treated with a Chêneau brace. With an average age of 12.5 years old and a mean Risser sign of 0.9, the initial major Cobb angle was 36.8 degrees corrected to 25.9 degrees in the brace (31.1 % of the primary correction), and the major torsion angle was 16.8 degrees corrected to 12.9 degrees in the brace (22.2 % of the primary correction). A total of 37 patients have finished the treatment with a mean follow-up of 16.8 months. For this group, the initial Cobb and torsion angles were not significantly changed (36.4 degrees Cobb to 34.1 degrees Cobb at follow-up, and 16.9 degrees Perdriolle to 15.7 degrees Perdriolle at follow-up). The proportion of patients without progression greater than 5 degrees Cobb (n = 20) and with an improved final Cobb angle (n = 10) was greater than failures (n = 7). However, due to the catastrophic nature of some progressions, which generally coincide with a high Cobb angle right from the start, with low primary correction, and with non-compliance, the final Cobb angle showed a slight

tendency to decrease but without reaching high significance. These results demonstrate that the Chêneau brace can effectively prevent the progression of Cobb and torsion angles, even in cases of bad prognosis.

Weiss et al (2006) stated that in patients with idiopathic scoliosis (IS), reduced thoracic kyphosis and reduced lumbar lordosis frequently occur in correlation with the lateral spinal curvature. Normalization of the sagittal profile and hyper-correction of the deviation in frontal and coronal plane are the main issues of the latest concept of bracing. The purpose of this study was to investigate the influence of of sagittal counter forces (SCF) on the scoliotic deformity. A case series of 4 patients with IS treated with 2 braces designed to improve the sagittal profile (Rigo-System-Chêneau-brace and with a sagittal counter force brace, SCF-brace). The short-term effect (30 mins) of both braces was evaluated using surface topography (Formetric surface topography system, Diers International, Wiesbaden). One patient (Cobb angle 92 degrees) showed no short-term correction in the frontal and coronal planes; others (Cobb angles between 39 and 48 degrees) exhibited valuable correction in frontal and coronal planes. There was no short-term correction in the sagittal plane for either brace. The authors concluded that the application of SCF seems to have similar short-term effects as 3-D correction and should be addressed more in future concepts of scoliosis bracing.

Grivas and Kaspiris (2010) stated that there is a lack of a systematic examination of the braces commonly used in Europe. Thus, the objective of this report was the description of the European braces widely used. The history, design rationale, indications, biomechanics, outcomes and comparison between some braces were reported. Chêneau Brace is used in France and other European Countries. There are 2 Cheneau derivatives,

namely the RSC brace used in Spain and the ScoliOlogiC "Chêneau light" used in Germany. The Lyonnaise brace is used in France and Italy. The Dynamic Derotating brace is used in Greece. The TriaC brace is used in the Netherlands. The Sforzesco brace based on the SPoRT concept and the Progressive Action Short brace are used in Italy. Correction of spinal deformities is achieved in conservative treatment with passive and active brace mechanisms. The mode of operation of modern braces is in accordance with various principles of correction, namely active or passive extension with the aid of a neck ring and correction by lateral pads, lateral pressure according to 3-point principle, compression, bending the trunk towards the opposite side, active bracing and correction by means of pressure exerted by bands during movement and by means of metallic blades.

The Risser jacket has been used to correct scoliosis for many years. The Research Committee of the American Orthopaedic Association's report on end-result study of the treatment of idiopathic scoliosis (Shands et al, 1941) discussed the use of the Risser jacket to correct the curve prior to fusion in 149 patients. Clinical improvement of the rotation deformity was observed following correction with the Risser jacket in 48 % of the 126 patients on whom these data were available. In addition, the best clinical appearances of the back were obtained in the group treated by correction in the Risser jacket and spine fusion. James (1952) noted that correction of the primary curvature in scoliotic patients is achieved by the use of the Risser turnbuckle jacket, the most effective method yet devised. Furthermore, a review on infantile scoliosis by Lakshmanan and colleagues (2009) stated that management with orthosis is necessary when the curve is considered to be progressive or if a compensatory curve has developed. Various types of orthosis are available for children younger than 3 years. The most commonly used orthoses include the hinged Risser jacket, the

Milwaukee brace, and the Boston brace. The brace should be used for 23.5 hours a day and should be removed only for exercises and swimming. It needs to be used until skeletal maturity is attained, because curves usually do not progress after skeletal maturity; however, curves may progress in spite of using a brace.

Negrini and associates (2003) performed a systematic review of the literature to verify the effectiveness of physical exercises in the treatment of AIS. These investigators carried out a search of different databases, and a hand-search of the non-indexed pertinent literature, and found 11 papers: none of the studies was randomized, 6 were prospective, 7 were controlled, and 2 compared their results to historical controls; 1 paper had both a prospective design and a concurrent control group. The methodological quality of the retrieved studies was reviewed and found to be very poor. With one exception, the published studies demonstrated the effectiveness of physical exercises in reducing both the rate of progression and the magnitude of the Cobb angle at the end of treatment. However, being of poor quality, the literature failed to provide solid evidence for or against the efficacy of physical exercises in the treatment of AIS.

Negrini et al (2008) examined if the indication for treatment with specific exercises for AIS has changed in recent years. A bibliographic search with strict inclusion criteria (patients treated exclusively with exercises, outcome Cobb degrees, all study designs) was performed on the main electronic databases and through extensive manual searching. These researchers retrieved 19 studies, including 1 randomized controlled trial (RCT) and 8 controlled studies; 12 studies were prospective. A methodological and clinical evaluation was performed. The 19 papers considered included 1,654 treated patients and 688 controls. The RCT (highest-quality study) compared 2 groups of 40

patients, showing an improvement of curvature in all treated patients after 6 months. These investigators found 3 papers on Scoliosis Intensive Rehabilitation (Schroth), 5 on extrinsic autocorrection-based methods (Schroth, side-shift), 4 on intrinsic autocorrection-based approaches (Lyon and SEAS) and 5 with no autocorrection (3 asymmetric, 2 symmetric exercises). Apart from 1 (no autocorrection, symmetric exercises, very low methodological quality), all studies confirmed the efficacy of exercises in reducing the progression rate (mainly in early puberty) and/or improving the Cobb angles (around the end of growth). Exercises were also shown to be effective in reducing brace prescription. The authors concluded that in 5 years, 8 more papers have been published to the indexed literature coming from throughout the world (Asia, the United States, Eastern Europe) and proving that interest in exercises is not exclusive to Western Europe.

The review by Negrini and colleagues (2008) emphasized a RCT by Wan et al (2005) of exercise in idiopathic scoliosis. The article by Wan et al is in Chinese, but the description of the study by Negrini et al indicated that the study duration was 6 months, raising questions about the durability of results. Subjects in both the exercise group and control group improved from baseline (15 degrees in the exercise group and 7 degrees in the control group), and there is no report whether the differences between the 2 groups at the end of treatment were statistically significant. Furthermore, the Cobb angles at initiation of therapy (25 degrees in the exercise group and 24 degrees in the control group) were within a range for which children are often managed with observation.

Furthermore, the American Academy of Orthopedic Surgeons (2007) stated that exercise programs have not been found to be effective treatments for scoliosis. The

National Institute of Arthritis and Musculoskeletal Diseases of the National Institutes of Health (2008) stated that exercise has not been shown to prevent curve progression. Addtionally, Schiller and co-workers (2010) stated that although numerous non-operative methods have been attempted, including exercise, only bracing is effective in preventing curve progression and the subsequent need for surgery.

Spinal Unloading Devices:

In a pilot study, Chromy and colleagues (2006) evaluated potential benefits of axial spinal unloading (LTX 3000 Lumbar Rehabilitation System) over a 3-month period. A total of 5 adolescent girls with scoliosis were enrolled in the study. Three laboratory sessions: (i) initial baseline, (ii) immediately after 3-month treatment period (axial unloading by using LTX 3000 for 2 10-min treatments daily), and (iii) 1-month post-treatment. Initial baseline postural data were obtained from 2 sets of radiographs (standing antero-posterior [AP] and lateral, sitting AP and lateral), back range of motion (ROM) measurements, and numeric pain scales. The following were assessed: static postural changes; potential functional benefits; and therapeutic compliance. All subjects elicited reductions in lumbar Cobb angles immediately after 3 months of treatment; initial average scoliotic curves of 13.7 degrees were reduced 42 % to 8 degrees (alpha = 0.05, p = 0.004). Additionally, such reductions were evident 1 month post-treatment; average original curves were reduced by 27 %. Subjects' ROM and lumbar lengthening were not significantly altered by this therapeutic protocol. Reported subject compliance was high (95 %). The authors concluded that the LTX 3000 is a potential adjunct therapy for the treatment of adolescent scoliosis. The findings of the present study need to be validated by randomized controlled trials with large sample size and long-term follow-up.

Vertebral Body Stapling:

Vertebral body stapling (VBS) is an alternative to bracing or spinal fusion for the treatment of progressive scoliosis. It is believed that for patients with progressive moderate scoliosis who are still growing, intervertebral body stapling of the outer (convex) side of the anterior spine (the side of the spine facing the chest) may keep the curve from progressing. With the convex growth plates held in check, continued development of the inner (concave) growth plates should stabilize the progression and may allow correction of deformity as the subject grows. This approach employs a special metal device that is clamp-shaped at body temperature, but can be straightened when subjected to cold temperatures and inserted into the spine. When warmed up, the staple returns to its clamp shape and supports the spine.

Betz and colleagues (2003) reported the feasibility, safety, and utility of VBS without fusion as an alternative treatment for adolescent idiopathic scoliosis. These researchers retrospectively reviewed 21 patients (27 curves) with adolescent idiopathic scoliosis treated with VBS. Patients were immature as defined by Risser sign less than or equal to 2. The procedure was safe, with no major complications and three minor complications. One patient had an intra-operative segmental vein bleed resulting in an increased estimated blood loss of 1,500 ml as compared to the average estimated blood loss of 247 ml for all patients. One patient had a chylothorax and one pancreatitis. No patient has had a staple dislodge or move during the follow-up period (mean 11 months, range of 3 to 36 months), and no adverse effects specifically from the staples have been identified. Utility (defined as curve stability) was evaluated in 10 patients with stapling with greater than 1-year follow-up (mean of 22.6 months) and pre-operative curve less than 50 degrees. Progression of

greater than or equal to 6 degrees or beyond 50 degrees was considered a failure of treatment. Of these 10 patients, 6 (60 %) remained stable or improved and 4 (40 %) progressed. One of 10 (10 %) in the stapling group had progressed beyond 50 degrees and went on to fusion. Six patients required stapling of a second curve, 3 as part of the primary surgery, and 3 as a second stage, because a second untreated curve progressed. The results need to be considered with caution, as the follow-up was short. The authors concluded that the data showed that VBS for the treatment of scoliosis in the adolescent was feasible and safe in this group of 21 patients. In the short-term, stapling appears to have utility in stabilizing curves of progressive adolescent idiopathic scoliosis.

Betz et al (2005) reported the findings of 39 consecutive patients who have had VBS of 52 curves (26 patients with one curve stapled and 13 patients with two curves). For patients who were 8 years or older with less than 50 degrees pre-operative curve and a minimum 1-year follow-up, coronal curve stability was 87 % when defined by progression less than or equal to 10 degrees. Fusion was necessary in 2 patients. No curves less than 30 degrees at the time of stapling progressed greater than or equal to 10 degrees. Major complications occurred in 1 patient (2.6 %, diaphragmatic hernia) and minor complications occurred in 5 patients (13 %). The authors concluded that further follow-up of treated patients and more research into effectiveness and indications are needed.

Cunningham et al (2005) noted that standard interventions for adolescents and adults, including spinal deformity correction and fusion, may not be appropriate for young patients with considerable growth remaining. Alternative surgical options that provide deformity correction and protect the growth remaining in the spine are needed to treat this

population of patients. Several groups have reported advances in the field of deformity spine surgery. Updated findings concerning the successful implementation of growing rods have revived this technique as a viable option for preserving near normal growth of the spine. New techniques have also been recently described, including vertebral stapling that produces asymmetric and corrective growth of the concavity of a deformity, and vertical expandable prosthetic titanium rib instrumentation that indirectly corrects spine deformity and protects spine growth remaining to treat an associated thoracic insufficiency syndrome. The authors concluded that new techniques and instrumentation allow the treatment of this challenging patient population to approach the goals of deformity correction and maintenance with preservation of potential growth. Preliminary outcomes from the different techniques are promising, but further investigation, including long-term follow-up, is needed.

In an assessment of VBS for the treatment of idiopathic scoliosis, the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (2005) concluded that limited evidence exists on the safety and effectiveness of VBS. Current evidence of this procedure is limited to small patient numbers and short-term follow-up. Furthermore, long-term safety and effectiveness data from prospective, RCTs will be needed before VBS can be widely accepted.

Guille et al (2007) stated that the recent investigations of convex anterior VBS have offered promising early results with use of improved implants and techniques. The use of a shape memory alloy staple tailored to the size of the vertebral body, the application of several staples per level, the instrumentation of the Cobb levels of all curves, and the employment of minimally invasive thoracoscopic approaches all offer substantial improvements over previous fusionless techniques.

Patient selection may also play a role in the current success of these fusionless treatments, with perhaps the ideal candidates for this intervention possessing smaller and more flexible curves. However, the authors stated that long-term results of the effects on the instrumented motion segments and adjacent spine are not yet available.

Betz et al (2010), in a retrospective review, reported the results of vertebral body stapling (VBS) with a minimum 2-year follow-up in 28 patients with idiopathic scoliosis. Inclusion criteria included Risser 0 or 1 and coronal curve measuring between 20 and 45 degrees. There were 26 thoracic and 15 lumbar curves, and average follow-up was 3.2 years. The procedure was considered a success if curves corrected to within 10 degrees of preoperative measurement or decreased greater than 10 degrees. Thoracic curves measuring less than 35 degrees had a success rate of 77.7%. Curves which reached less than or equal to 20 degrees on first erect radiograph had a success rate of 85.7%. Flexible curves with greater than 50% correction on bending films had a success rate of 71.4%. Of the 26 thoracic curves, 4 (15%) showed correction greater than 10 degrees. Kyphosis improved in 7 patients with preoperative hypokyphosis (less than 10 degrees of kyphosis from T5 – T12). 83.% of patients had remaining normal thoracic kyphosis of 10 to 50 degrees. Lumbar curves demonstrated a success rate of 86.7%. Four of the 15 lumbar curves (27%) showed correction greater than 10 degrees. Major complications included rupture of an unrecognized congenital diaphragmatic hernia (one patient) and curve overcorrection (one patient). Two minor complications included superior mesenteric artery syndrome (one patient) and atelectasis due to a mucous plug (one patient). There were no instances of staple dislodgment or neurovascular injury. In conclusion, analysis of patients with idiopathic scoliosis with high-risk progression treated with VBS and a minimum 2-year

follow-up showed a success rate of 87% in all lumbar curves and in 79% of thoracic curves less than 35 degrees. Thoracic curves greater than 35 degrees were not successful and require alternative treatments. Of the 63 patients with IS age at surgery 7-15 , 57 had x-rays at most recent follow-up that allowed for visualization of iliac crest. Skeletal maturity was defined as having a Risser score $\geq$ 4. Among the thoracic curves, 12 of the successful outcomes were $\geq$ Risser 4 while 5 of the failures were $\geq$ Risser 4. Thus, the success rate for mature thoracic curves was 71% (12/17). Among the lumbar curves, 17 of the successful outcomes were $\geq$ Risser 4 while 2 of the failures were $\geq$ Risser 4. Thus, the success rate for mature lumbar curves was 89% (17/19).

In a single-surgeon, retrospective case-series study, Bumpass et al (2015) described clinical and radiographic outcomes of patients undergoing VBS, with the goal of learning if VBS is a safe and effective alternative to bracing for treating moderate IS in the growing pediatric patient. Existing studies stated successful curve control rates equivalent to bracing, but the majority of reports had come from a single institution. All IS patients who underwent VBS by 1 surgeon were included. Indications were brace intolerance and a structural coronal curve of 25° to 40°. Proportional nitinol staples were used in all cases. Pre- and post-operative radiographs, pulmonary function testing, and physical exam measurements were serially recorded. Vertebral body stapling was performed on 35 patients (28 females, 7 males) with mean age 10.5 years (range of 7.0 to 14.6). A total of 31 patients (33 stapled curves) completed follow-up. Pre-operative Risser grade was 0 in 31 patients, 1 in 1 patient, and 2 in 3 patients. Stapled curves were controlled with less than 10° of progression in 61 % of cases. Curves less than 35° had a control rate of 75 %, and patients less than 10 years had a 62 % curve control rate; 11patients (31 %) required subsequent fusions; 2 curves (6 %) over-corrected. Pre-operative supine

flexibility greater than 30 % was predictive of ultimate curve control. No neurologic complications were encountered; 5 patients (14 %) developed small pneumothoraxes. The authors concluded that this series contained the most patients and longest follow-up reported for VBS. They noted that successful curve control was achieved less frequently than in previous reports, particularly in patients less than 10 years. This study provided Level IV evidence.

Chiropractic Manipulation and Exercise:

In a systematic literature review of non-surgical treatment in adult scoliosis, Everett and Patel (2007) stated that the evidence on the use of chiropractic manipulation for adult scoliosis is very weak.

Hrysomallis and Goodman (2001) noted that exercise has been promoted in an attempt to correct postural deviations, such as excessive lumbar lordosis, scoliosis, kyphosis, and abducted scapulae. One of the assumed causes of these conditions is a weak and lengthened agonist muscle group combined with a strong and tight antagonist muscle group. Strengthening and stretching exercises have been prescribed accordingly. It is implied that strengthening exercises will encourage adaptive shortening of the muscle-tendon length, reposition skeletal segments, and produce static posture realignment. A review of the literature has found a lack of reliable, valid data collected in controlled settings to support the contention that exercise will correct existing postural deviations. Likewise, objective data to indicate that exercise will lead to postural deviations are lacking. It is likely that exercise programs are of insufficient duration and frequency to induce adaptive changes in muscle-tendon length. Additionally, any adaptations from restricted range-of-movement exercise would

likely be offset by daily living activities that frequently require the body segments to go through full ranges of motion.

Mooney and Brigham (2003) reported on the use of progressive resistive exercise in adolescents with scoliosis. A total of 20 adolescent patients (18 girls and 2 boys) with scoliosis ranging from 15 degrees to 41 degrees in their major curve were treated with a progressive resistive training program for torso rotation. All patients demonstrated an asymmetry of rotation strength measured on specialized equipment, and surface electrode electromyograms showed inhibition of lumbar paraspinal muscles. Sixteen of 20 patients demonstrated curve reduction, and no patient showed an increase in curve. These results would need to be replicated in a larger trial. The durability and effectiveness compared with bracing would also need to be evaluated.

In a pilot study, McIntire and colleagues (2008) examined treatment of adolescent idiopathic scoliosis with quantified trunk rotational strength training. Patients received a 4-month supervised followed by a 4-month home trunk rotational strength training program. Trunk rotational strength was measured in both directions at 5 positions at baseline, 4 months, and 8 months. Patients were followed clinically. A total of 15 patients (12 females and 3 males), with an average age of 13.9 years and an average main Cobb of 33 degrees were enrolled. At baseline, there was no significant asymmetry. After 4 months of supervised strength training, involving an average of 32 training sessions, each lasting about 25 mins, their strength had significantly increased by 28 % to 50 % ($p < 0.005$ to $p < 0.001$). After 4 months of unsupervised home strength training their strengths were unchanged. The 3 patients with baseline curves of 50 to 60 degrees all had main or compensatory curve progression and 2 had surgery. For

patients with 20 to 40-degree curves, survivorship from main curve progression of greater than or equal to 6 degrees was 100 % at 8 months, but decreased to 64 % at 24 months. The authors concluded that quantified trunk rotational strength training significantly increased strength. It was not effective for curves measuring 50 to 60 degrees. It appeared to help stabilize curves in the 20 to 40-degree ranges for 8 months, but not for 24 months. Periodic additional supervised strength training may help the technique to remain effective, although additional experimentation will be necessary to determine this.

Whole Body Vibration:

Li and colleagues (2011) stated that numerical techniques were used to study the vibration response of idiopathic scoliosis patients with single thoracic curve. These researchers analyzed the dynamic characteristics of the idiopathic scoliotic spine under the whole body vibration (WBV) condition. The influence of the upper body mass was also studied. The relationship between the WBV and the spinal disorders has been investigated using finite element method. However, the dynamic response features of the scoliotic spine to the vibration were poorly understood. The resonant frequencies of the scoliotic spine and the effects of the body weight were studied using a finite element model described previously. Modal and harmonic analysis was conducted. The amplitudes of 6 fundamental vertebral movements around the long, coronal and sagittal axis were quantified in the frequency range of 1 to 35 Hz. The vibration-induced rotation amplitudes of the apex of the thoracic deformity were higher than that of the lumbar segments. The apical vertebrae had the greatest rotation amplitudes at 2 and 8 Hz, and the largest lateral translation amplitudes at 16 Hz. Vibration could cause large lateral flexion amplitudes in the apex of the thoracic deformity. The apical vertebrae had the largest

side flexion amplitudes at 6 Hz. Increasing upper body mass could not change resonant frequency of vibration-induced lateral translation and rotation around the long axis of the apical vertebrae. The authors concluded that the scoliotic spine is more sensitive to vibration than the normal spine. For a patient with single thoracic curve, long-term WBV may do more harm to the thoracic deformity than to the lower lumbar segments. Axial cyclic loads applied to an already deformed spine may cause further rotational and scoliotic deformity. Patients with idiopathic scoliosis are more likely to suffer from vibration-induced spinal disorders than those by normal persons.

Genetic Tests:

Adolescent idiopathic scoliosis is a lateral spinal curvature observed in children 10 years of age or older, and approximately 100,000 new cases of AIS are diagnosed annually. Of these most are small curvatures of less than 15 to 20 degrees requiring only routine observation for progression. If a curve reaches 20 to 40 degrees, orthotic bracing is used to prevent further progression. If the bracing is unsuccessful and the curve progresses beyond 40 degrees surgical correction may be required. Only about 7 to 10 % of patients require braces and only 1 to 4% require surgery. Patients identified with AIS are periodically monitored for progression of the curve using various methods based on the angular relationships of the vertebrae and assessment of skeletal maturity. Recently a genetically-based test has been developed that is supposed to identify those individuals with the highest risk for curve progression. Those with a low-risk would require less frequent monitoring and x-ray exposure, while those at higher risk would be checked more frequently. The ScoliScore™ AIS Prognostic Test is being offered by Axial Biotech, Inc., and is intended for children between 9 and 13 years of age with a primary diagnosis of AIS and a

mild spinal curvature (defined as less than 25 degrees) and who are of Caucasian ethnicity. The test examines a total of 53 genetic markers and converts the result into a risk score using a proprietary software algorithm. A score of 1 to 50 constitutes low-risk for curve progression, 51 to 180 intermediate-risk, and 181 to 200 high-risk.

No articles were found in the peer-reviewed medical literature to independently assess the ScoliScore™ test for analytic validity, clinical validity or clinical utility. A review article by Ogilvie (2010) described how studies of families have been used to determine the inherited nature of AIS. The article declared the test has been validated in Caucasian girls and boys but is not validated in Asians or African-Americans. No details of any clinical trials were discussed. Without clinical trials information in the scientific literature it is not possible to reach conclusions on health outcomes. There is a substantial body of literature addressing evaluation of curve progression by standard methods but none of these studies or reviews mentioned genetic testing. As no articles are currently available in the literature, it is not possible to determine if ScoliScore™ improves net health outcomes. Nor have there been any comparison studies to address whether the use of the genetic test is at least as effective as standard monitoring.

Ward et al (2010) developed and tested the negative predictive value of a prognostic DNA test for AIS and established clinically meaningful endpoints for the test. Logistic regression was used to develop an algorithm to predict spinal curve progression incorporating genotypes for 53 single nucleotide polymorphisms (SNPs) and the patient's presenting spinal curve (Cobb angle). Three cohorts with known AIS outcomes were selected to reflect intended-use populations with various rates of AIS progression: 277 low-risk females representing a screening cohort, 257 females

representing higher risk patients followed at referral centers, and 163 high-risk males. DNA was extracted from saliva, and genotypes were determined using TaqMan assays; AIS Prognostic Test scores ranging from 1 to 200 were calculated. Low-risk scores (less than 41) had negative predictive values of 100 %, 99 %, and 97 %, respectively, in the tested populations. In the risk model, these researchers used cut-off scores of 50 and 180 to identify 75% of patients as low-risk (less than 1 % risk of progressing to a surgical curve), 24 % as intermediate-risk, and 1 % as high-risk. The authors concluded that prognostic testing for AIS has the potential to reduce psychological trauma, serial exposure to diagnostic radiation, unnecessary treatments, and direct and indirect costs-of-care related to scoliosis monitoring in low-risk patients. They stated that further improvements in test performance are expected as the optimal markers for each locus are identified and the underlying biologic pathways are better understood. The validity of the test applies only to white AIS patients; versions of the test optimized for AIS patients of other races have yet to be developed.

Liu et al (2010) examined the association between the promoter polymorphisms of matrix metalloproteinase (MMP)-3 (-1171 5A/6A rs3025058) and interleukin (IL)-6 genes (-174G/C rs1800795) and AIS in a Chinese Han population. A total of 487 Chinese girls with AIS and 494 healthy age-matched adolescent girls were recruited consecutively during a 3-year period. Statistical analysis of genotype frequencies between AIS patients and normal controls were performed by Chi-test. In this association study of the MMP-3 polymorphism and the risk of scoliosis, no significant difference was found between cases and controls, both in term of allelic association (6A: 81.2 % in cases versus 81.8 % in controls, 5A: 18.8 % in cases versus 18.2 % in controls, p = 0.745) or genotype association (6A/6A: 65.9 % in cases versus 66.2 % in controls, 5A/6A: 30.6 % in cases versus

31.2 % in controls, and 5A/5A: 3.5 % in cases versus 2.6 % in controls; p = 0.733). Among AIS patients, the maximal Cobb angles were also not different among MMP-3 genotypes (6A/6A: 31.1 degrees +/- 9.7 degrees, 5A/6A: 29.1 degrees +/- 10.5 degrees, and 5A/5A: 29.4 degrees +/- 11.2 degrees; p = 0.392). As for IL-6 polymorphism, -174G/C polymorphism was not found in the Chinese AIS patients, and all 100 AIS patients and 100 normal controls were found to carry the G/G wild type. The authors concluded that these findings did not find any significant association of promoter polymorphisms of the MMP-3 (-1171 5A/6A rs3025058) and IL-6 gene (-174G/C rs1800795) with AIS. The results indicated that the MMP-3 promoter polymorphism is not associated with AIS in the Chinese population. They noted that further studies, however, are needed to rule out the potential association with other promoter polymorphisms in IL-6.

Sharma et al (2011) noted that AIS is an unexplained and common spinal deformity seen in otherwise healthy children. Its pathophysiology is poorly understood despite intensive investigation. Although genetic underpinnings are clear, replicated susceptibility loci that could provide insight into etiology have not been forthcoming. To address these issues, these investigators performed genome-wide association studies (GWAS) of approximately 327,000 SNPs in 419 AIS families. They found strongest evidence of association with chromosome 3p26.3 SNPs in the proximity of the CHL1 gene ($p < 8 \times 10(-8)$ for rs1400180). They genotyped additional chromosome 3p26.3 SNPs and tested replication in 2 follow-up case-control cohorts, obtaining strongest results when all 3 cohorts were combined (rs10510181 odds ratio (OR) = 1.49, 95 % confidence intervals (CI): 1.29 to 1.73, $p = 2.58 \times 10(-8)$), but these were not confirmed in a separate GWAS. CHL1 is of interest, as it encodes an axon guidance protein related to Robo3. Mutations in

the Robo3 protein cause horizontal gaze palsy with progressive scoliosis (HGPPS), a rare disease marked by severe scoliosis. Other top associations in the authors' GWAS were with SNPs in the DSCAM gene encoding an axon guidance protein in the same structural class with Chl1 and Robo3. These researchers additionally found AIS associations with loci in CNTNAP2, supporting a previous study linking this gene with AIS. Cntnap2 is also of functional interest, as it interacts directly with L1 and Robo class proteins and participates in axon pathfinding. The authors concluded that these findings suggested the relevance of axon guidance pathways in AIS susceptibility, although these results require further study, particularly given the apparent genetic heterogeneity in this disease.

Huang and colleagues (2011) examined if the matrix metalloproteinase 9 gene (MMP9) polymorphism is associated with the onset or progression of AIS in Chinese Han female. Three SNPs (rs17576, rs2250889, rs1805088) were genotyped through TaqMan-based real-time polymerase chain reaction (PCR) assay in 190 AIS patients and 190 controls, all of whom were females from Chinese Han population with matched age. Analyses performed included Hardy Weinberg equilibrium test, Pearson chi-square test, Logistic regression analysis, linkage disequilibrium analysis and haplotype analysis. The mean maximum Cobb angles with different genotypes in case-only dataset were also compared. All 3 SNPs have reached Hardy-Weinberg equilibrium in the controls. Genotype and allele frequencies of all SNPs were found similar between cases and controls by Pearson chi-square test and Logistic regression. Genotype-phenotype analysis showed that patients with CC genotype in rs2250889 featured larger maximum Cobb angles. The authors concluded that MMP9 may not be a predisposition gene

of AIS in Han female. However, homozygous mutation in rs2250889 can render scoliosis more severe, implying that MMP9 defect may result in deterioration of AIS.

Xu and associates (2011) examined if the predisposition genes previously reported to be associated with the occurrence or curve severity of AIS may play a role in the effectiveness of brace treatment. A total of 312 AIS patients treated with bracing were enrolled in this study. The Cobb angle of the main curve was recorded at the beginning of brace treatment as well as at each follow-up. The patients were divided into 2 groups according to the outcome of brace treatment (success/failure). The failure of brace treatment was defined as a curve progression of more than 5 degrees compared to the initial Cobb angle or surgical intervention because of curve progression. Single nucleotide polymorphism sites in the genes for estrogen receptor α (ERα), estrogen receptor β (ERβ), tryptophan hydroxylase 1 (TPH-1), melatonin receptor 1B (MTNR1B) and matrillin-1 (MATN1), which were previously identified to be predisposition genes for AIS, were selected for genotyping by the PCR-RFLP method. Differences of genotype and allele distribution between the 2 groups were compared by the $\chi(2)$ test. A logistic regression analysis was used to figure out the independent predictors of the outcome of brace treatment. There were 90 cases (28.8 %) in the failure group and 222 cases (71.2 %) in the success group. Patients in the failure group were associated with the genotype GA (50.9 versus 17.9 % $p < 0.001$) and the G allele (27.1 versus 12.0 %, $p < 0.001$) at SNP rs9340799 of the ERα gene. Similarly, they were also associated with the genotype AT (33.3 versus 13.0 %, $p = 0.002$) and the A allele (16.7 versus 9.6 %, $p = 0.033$) at SNP rs10488682 of the TPH-1 gene. For MTNR1B, the difference of genotype distribution between the 2 groups was found to be statistically significant, while the difference of allele distribution between the 2 groups

was found to be marginally statistically significant; for the MATN1 and ERβ genes, these investigators found no significant differences of the genotype or allele distribution between the 2 groups. In the logistic regression analysis, ERα and TPH-1 were demonstrated to be independent factors predictive of bracing effectiveness. The authors concluded that ERα and TPH-1 might be potential genetic markers that could predict the outcome of brace treatment. Patients with the G allele at the rs9340799 site of the ERα gene and the A allele at the rs10488682 site of the TPH-1 gene are prone to be resistant to brace treatment.

Miller (2011) stated that idiopathic scoliosis is one of the most common complex genetic disorders of the musculo-skeletal system. The clinical parameters relating to onset, curve progression, and severity in relation to clinical prognosis and current treatment modalities have been defined, but do not address the cause of this disorder. In an effort to define causative genetic elements, multiple studies have delineated potential genetic loci that are statistically related to idiopathic scoliosis in a variety of populations. The question remains how future genetic testing and genomic profiling may be of aid in the therapeutic algorithms related to this disorder.

Thus, it seems that AIS is a complex disorder that result from the interaction of multiple genetic loci and the environment, however, the details of these interactions are unclear. Furthermore, an UpToDate review on "Treatment and prognosis of adolescent idiopathic scoliosis" (Scherl, 2012) does not mention the use of genetic testing.

In a review of management of idiopathic scoliosis published in the New England Journal of Medicine, Hresko (2013) commented on genetic testing for idiopathic scoliosis: “A genetic-screening test based on

identification of single-nucleotide polymorphisms to predict the risk of progression of mild idiopathic scoliosis to scoliosis that requires surgical treatment is commercially available, but it has not been independently validated. Data are currently lacking to indicate that genetic testing adds meaningfully to predictions made on the basis of skeletal maturity and curve magnitude".

Ogura et al (2013) examined if the association of 53 SNPs with curve progression reported in white patients with AIS are replicated in Japanese patients with AIS. These researchers recruited 2,117 patients with AIS with 10° or more (Cobb angle) of scoliosis curves. They were divided into progression and non-progression groups according to their Cobb angle. These investigators defined the progression of the curve as Cobb angle more than 50° for skeletally mature subjects and more than 40° for immature patients, subjects. They defined the non-progression of the curve as Cobb angle 50° or less only for skeletally mature subjects. Of the 2,117 patients, 1,714 patients with AIS were allocated to either the progression or non-progression group. These researchers evaluated the association of 53 SNPs with curve progression by comparing risk allele frequencies between the 2 groups. They evaluated the progression (n = 600) and non-progression (n = 1,114) subjects. Their risk allele frequencies were not different significantly. They found no replication of the association on AIS curve progression in any of the SNPs. The authors concluded that the associations of the 53 SNPs with progression of AIS curve are not definite. Moreover, they stated that large-scale association studies based on appropriate criteria for progression would be necessary to identify SNPs associated with the curve progression.

Tilley et al (2013) performed model-independent linkage analysis and tests of association for 22 SNPs in the CHD7 gene in 244 families of European descent with familial idiopathic scoliosis (FIS). This study was carried out to replicate an association between FIS and the CHD7 gene on 8q12.2 in an independent sample of families of European descent. Model-independent linkage analysis and intra-familial tests of association were performed on the degree of lateral curvature considered as a qualitative trait (with thresholds of greater than or equal to 10°, greater than or equal to 15°, greater than or equal to 20°, and greater than or equal to 30°) and as a quantitative trait (degree of lateral curvature). Results from the tests of associations from this study and the previous study were combined in a weighted meta-analysis. No significant results ($p < 0.01$) were found for linkage analysis or tests of association between genetic variants of the CHD7 and FIS in this study, failing to replicate the findings from the previous study. Furthermore, no significant results ($p < 0.01$) were found from meta-analysis of the results from the tests of association from this sample and from the previous sample. The authors concluded that no association between the 22 genotyped SNPs in the CHD7 gene and FIS within this study sample was found, failing to replicate the earlier findings. They stated that further investigation of the CHD7 gene and its potential association to FIS may be required.

Ryzhkov and associates (2013) performed a genetic association study of the transforming growth factor beta 1 (TGFB1) gene with AIS in Russian population. These researchers examined if common genetic polymorphisms C-509T (rs1800469) and Arg25Pro (rs1800471) of the TGFB1 gene are associated with susceptibility to AIS. A total of 600 unrelated adolescents from central Russia (Moscow) were recruited in this study, including 300 patients with AIS and 300 age- and sex-matched healthy adolescents. The

polymorphisms were genotyped by PCR-restriction fragment length polymorphism. The allele -509T and genotype -509TT of the TGFB1 gene were significantly associated with the increased risk of AIS in both females and males ($p < 0.01$). Logistic regression analysis has revealed a recessive model of the genetic association between polymorphism C-509T of the TGFB1 gene and AIS. Moreover, these investigators found sexual dimorphisms in the relationships of SNP C-509T of the TGFB1 gene with both the age of disease onset and curve severity: the polymorphism was found to determine both an early onset of scoliosis and the severity of curvature in females but not in males ($p < 0.05$). The authors concluded that the present study, for the first time, highlighted the importance of TGFB1 gene for the development and progress of AIS. These researchers hypothesized several mechanisms by which the TGFB1 gene may contribute to spinal deformity in patients with AIS.

In a meta-analysis, Liang et al (2014) investigated whether or not the rs11190870 polymorphism is associated with susceptibility to AIS in East Asian population. A systematic search of all relevant studies published through August 2013 was conducted using the MEDLINE, EMBASE, OVID, and ScienceDirect. Single nucleotide polymorphism of rs11190870 was evaluated. The included studies were assessed in the analysis of the following allele model: (a) T-allele versus C-allele for the allele level comparison; (b) TC+TT versus CC for dominant model of T-allele; (c) TT versus TC+CC for recessive model of T-allele, and (d) TT versus CC for extreme genotype. A total of 4 studies with 8,415 total participants (2,889 AIS patients and 5,526 controls), which were all East Asian population were eligible for inclusion. These investigators searched for genotypes T allele versus C allele, TT versus TC+ CC, TC + TT versus CC and TT versus CC in a fixed/random-effects model. The effect summary ORs) and 95 % CIs were obtained, which

shows significant association between rs11190870 and AIS in East Asian populations (all genetic models $p < 0.001$). Subgroup group analyses were conducted according to the gender. The results showed that a significant association between rs11190870 and AIS in female (all genetic models $p < 0.001$), but not in male (all genetic models $p > 0.05$). The authors concluded that the present meta-analysis demonstrated that the T allele of SNP rs11190870 may be a major susceptibility locus in the East Asian population with AIS, especially in female.

Zhang et al (2014) noted that several previous studies have evaluated the association between rs1149048 polymorphism in the matrilin-1 gene (MATN1) and the risk of AIS. However the results of those studies were inconsistent. These investigators conducted a meta-analysis to examine if rs1149048 polymorphism was involved in the risk of AIS and evaluated the associations in different ethnicities. Electronic databases, such as: PubMed, EMBASE, WANFANG databases in any languages up to December 2012 were searched to assess the association between rs1149048 polymorphism and AIS. Meta-analysis was performed by STATA 12.0 software to estimate the pooled OR and the 95 % CI. Finally 4 papers including 5 studies which involved 1,436 AIS patients and 1,879 controls were identified for this meta-analysis. The results showed that G allele of the rs1149048 was significantly associated with increased AIS risk [OR = 1.13, 95 % CI: 1.02 to 1.25), $p = 0.023$]. As for genotype (GG versus GA + AA), homozygous GG genotype was also found to be a risk factor of developing AIS. The subgroup meta-analysis results showed G allele and GG genotype were significantly associated with AIS in Asian group but not in Caucasian group. Neither Egger's test nor Begg's test found evidence of publication bias in current study ($p > 0.05$). The authors concluded that this meta-analysis found an overall significant association of rs1149048

polymorphism with risk of AIS, especially in Asian population. Moreover, they stated that the relationship between rs1149048 polymorphism and AIS in other ethnic population needed to be investigated.

Also, an UpToDate review on "Adolescent idiopathic scoliosis: Clinical features, evaluation, and diagnosis" (Scherl, 2014) states that "Genetic testing -- Adolescent idiopathic scoliosis (AIS) is a complex disorder that appears to result from the interaction of multiple genetic loci and the environment, but the details of these interactions are not fully understood".

ScoliScore Test:

In a replication association study that used genomic data generated from French-Canadian case and control cohorts, Tang et al (2015) examined if the 53 SNPs that were previously associated with spinal deformity progression in an American Caucasian cohort are similarly associated in French-Canadian population. Genomic data were collected from the French-Canadian population, using the Illumina HumanOmni 2.5M BeadChip. Fifty-two SNPs, tested in ScoliScore or in high linkage disequilibrium with SNPs in the test, were selected to evaluate their association with scoliosis generally, and with spinal curve progression. One SNP in ScoliScore, rs16909285, could not be evaluated in the Genome-Wide association study. None of the SNPs used in ScoliScore was associated with AIS curve progression or curve occurrence in French-Canadian population. These researchers evaluated 52 SNPs in severe patients by comparing risk allele frequencies with those in non-severe patients and with those in control individuals. There was no significant difference between the severe group and the non-severe group or between the severe group and the control group. The authors concluded that although the 52 SNPs studied here were previously associated with curve progression in an

American population of European descent, they found no association in French-Canadian patients with AIS. They stated that this second replication cohort suggested that the lack of association of these SNPs in a Japanese cohort is not due to ethnicity.

Melatonin Receptor 1B Gene (MTNR1B) (rs4753426 and rs10830963) Polymorphism Testing:

In a meta-analysis, Yang and colleagues (2015) examined if melatonin receptor 1B (MTNR1B) rs4753426 and rs10830963 polymorphisms are correlated with AIS. An systematic online search was performed using PubMed, EMBASE, Web of Science and the Cochrane Library to identify case-control studies investigating the relationship between MTNR1B rs4753426 and rs10830963 polymorphisms and the susceptibility of AIS. The pooled OR with 95 % CI was calculated to assess the associations, and subgroup meta-analyses were performed according to the ethnicity of the study populations. A total of 5 studies involving 2,395 cases and 3,645 controls met the inclusion criteria after assessment by 2 reviewers. Overall, no significant associations were found between MTNR1B rs4753426 polymorphism and AIS risk (C versus T: OR = 1.11, 95 % CI: 0.94 to 1.30, p = 0.21; CC versus TT: OR = 1.15, 95 % CI: 0.97 to 1.36, p = 0.12; CT versus TT: OR = 1.14, 95 % CI: 0.97 to 1.35, p = 0.10; CC/CT versus TT: OR = 1.14, 95 % CI: 0.98 to 1.33, p = 0.09; CC versus CT/TT: OR = 1.10, 95 % CI: 0.84 to 1.45, p = 0.48), as well as the MTNR1B rs10830963 polymorphism (G versus C: OR = 0.99, 95 % CI: 0.88 to 1.12, p = 0.91; GG versus CC: OR = 0.99, 95 % CI: 0.74 to 1.33, p = 0.96; CG versus CC: OR = 1.00, 95 % CI: 0.84 to 1.18, p = 0.88; GG/CG versus CC: OR = 0.99, 95 % CI: 0.84 to 1.17, p = 0.93; GG versus CG/CC: OR = 0.99, 95 % CI: 0.75 to 1.30, p = 0.92). When stratified by ethnicity, there were no significant associations between MTNR1B rs4753426 and MTNR1B rs10830963 polymorphisms and AIS risk in either Asian or Caucasian

populations. The authors concluded that MTNR1B rs4753426 and MTNR1B rs10830963 polymorphisms are not obviously associated with risk of AIS in either Asian populations or Caucasian populations.

The CLEAR Protocol:

The CLEAR protocol for treating scoliosis consists of 3 components: (i) Mix, (ii) Fix, and (iii) Set. The objective of the first part of the protocol (Mix) is to warm up the spine, and prepare it for the rest of the treatment. In this portion of the protocol the patient performs several activities to warm up and loosen up the spine. These activities include the wobble chair, and different tractioning devices designed put motion into the spine. The second part of the treatment protocol (Fix) entails chiropractic adjustments. Chiropractors also perform other modalities that begin to cause correction of the spinal curvatures. During the last part of the program (Set), the patient receives several treatments that are designed to stabilize the spine in a more corrected position. **http://www.clear-institute.org/TheCLEARScoliosisMethod/tabid/876/Default.aspx (http://www.clear-institute.org/TheCLEARScoliosisMethod/tabid/876/Default.aspx)**

There is currently insufficient evidence that chiropractic or osteopathic manipulation is effective in treating scoliosis.

In a systematic review, Romano and Negrini (2008) verified the evidence on the effectiveness of manual therapy in the treatment of adolescent idiopathic scoliosis. These investigators included in the term manual therapy all the manipulative and generally passive techniques performed by an external operator. In a more specific meaning, osteopathic, chiropractic and massage techniques have been considered as manipulative therapeutic methods. They performed

systematic researches in Medline, Embase, Cinhal, Cochrane Library, Pedro with the following terms: idiopathic scoliosis combined with chiropractic; manipulation; mobilization; manual therapy; massage; osteopathy; and therapeutic manipulation. The criteria for inclusion were as follows: Any kind of research; diagnosis of adolescent idiopathic scoliosis; patients treated exclusively by one of the procedures established as a standard for this review (chiropractic manipulation, osteopathic techniques, massage); and outcome in Cobb degrees. These researchers founded 145 texts, but only 3 papers were relevant to this study. However, none of the 3 satisfied all the required inclusion criteria because they were characterized by a combination of manual techniques and other therapeutic approaches. The authors concluded that the lack of any kind of serious scientific data prevented them from making any conclusion on the effectiveness of manual therapy for the treatment of adolescent idiopathic scoliosis.

Canavese and Kaelin (2011) noted that the strategy for the treatment of idiopathic scoliosis depends essentially upon the magnitude and pattern of the deformity, and its potential for progression. Treatment options include observation, bracing and/or surgery. During the past decade, several studies have demonstrated that the natural history of adolescent idiopathic scoliosis can be positively affected by non-operative treatment, especially bracing. Other forms of conservative treatment, such as chiropractic or osteopathic manipulation, acupuncture, exercise or other manual treatments, or diet and nutrition, have not yet been proven to be effective in controlling spinal deformity progression, and those with a natural history that is favorable at the completion of growth. Observation is appropriate treatment for small curves, curves that are at low-risk of progression, and those with a natural history that is favorable at the completion of growth. Indications for brace treatment are a growing child

presenting with a curve of 25° to 40° or a curve less than 25° with documented progression. Curves of 20° to 25° in patients with pronounced skeletal immaturity should also be treated.

Gleberzon et al (2012) conducted a search of the literature between 2007 and 2011 investigating the use of spinal manipulative therapy (SMT) for pediatric health conditions and performed a systematic review of eligible retrieved clinical trials. The Index of Chiropractic Literature and PubMed were electronically searched using appropriate search words and MeSH terms, respectively, as well as reference tracking of previous reviews. Studies that met the inclusion criteria were evaluated using an instrument that assessed their methodological quality. A total of 16 clinical trials were found that met the inclusion criteria and were scored. Six clinical trials investigated the effectiveness of SMT on colic, 2 each on asthma and enuresis, and 1 each on hip extension, otitis media, suboptimal breastfeeding, autism, idiopathic scoliosis and jet lag. None investigated the effectiveness of SMT on spinal pain. The authors concluded that many studies reviewed suffered from several methodological limitations. They stated that further research is needed in this area of chiropractic health care, especially with respect to the clinical effectiveness of SMT on pediatric back pain.

Also, an UpToDate review on "Treatment and prognosis of adolescent idiopathic scoliosis" (Scherl, 2013) states that "Options for treatment include observation, bracing, and surgery, as discussed below [2-6]. Physical therapy, chiropractic treatment, electrical stimulation, and biofeedback have been shown to be ineffective".

Vertebral Body Tethering:

Samdani et al (2014) reported the 2-year results of the initial cohort undergoing anterior vertebral body tethering (VBT). After obtaining institutional review board approval, these researchers retrospectively reviewed their first 11 consecutive patients who underwent anterior VBT with 2-year follow-up. They collected pertinent pre-operative, intra-operative, and most recent clinical and radiographical data. Student t-test and Fisher exact test were utilized to compare different time-points. Eleven patients with thoracic idiopathic scoliosis (8 females) were identified, with a mean age of 12.3 ± 1.6 years. Pre-operatively, all were skeletally immature (Sanders mean = 3.4 ± 1.1; Risser mean = 0.6 ± 1.1). All underwent tethering of an average of 7.8 ± 0.9 (range of 7 to 9) levels, with the most proximal being T5 and the most distal L2. Pre-operative thoracic Cobb angle averaged 44.2 ± 9.0° and corrected to 20.3 ± 11.0° on first erect, with progressive improvement at 2 years (Cobb angle = 13.5 ± 11.6°, % correction = 70 %; $p < 0.00002$). Similarly, the pre-operative lumbar curve of 25.1 ± 8.7° demonstrated progressive correction (first erect = 14.9 ± 4.9°, 2 year = 7.2 ± 5.1°, % correction = 71 %; $p < 0.0002$). Thoracic axial rotation as measured by a scoliometer went from 12.4 ± 3.3° pre-operatively to 6.9 ± 3.4° at the most recent measurement ($p < 0.01$). No major complications were observed. As anticipated, 2 patients returned to the operating room at 2 years post-operatively for loosening of the tether to prevent over-correction. The authors concluded that anterior VBT is a promising technique for skeletally immature patients with idiopathic scoliosis. This technique can be performed safely and can result in progressive correction. They stated that further study with longer term follow-up will hopefully elucidate the potential risks and benefits of this innovative technology.

The same group of investigators (Samdani et al, 2015) also published 1-year results of anterior VBT for more patients (n = 32). Clinical and radiographic data were retrospectively analyzed. They reviewed 32 patients who underwent thoracic VBT with a minimum 1-year follow-up. Pertinent clinical and radiographic data were collected. ANOVA, Student's t-test and Fisher's exact test were utilized to compare different time-points. A total of 32 patients with thoracic idiopathic scoliosis (72 % female) with a minimum 1-year follow-up were identified; mean age at surgery was 12 years. All patients were considered skeletally immature pre-operatively; mean Risser score 0.42, mean Sanders score 3.2. Patients underwent tethering of an average of 7.7 levels (range of 7 to 11). Median blood loss was 100 cc. The mean pre-operative thoracic curve magnitude was 42.8° ± 8.0°, which corrected to 21.0° ± 8.5° on first erect and 17.9° ± 11.4° at most recent. The pre-operative lumbar curve of 25.2° ± 7.3° demonstrated progressive correction (first erect = 18.0° ± 7.1°, 1 year = 12.6° ± 9.4°, $p < 0.00001$). Thoracic axial rotation measured 13.4° pre-operatively and 7.4° at the most recent measurement ($p < 0.00001$); 1 patient experienced prolonged atelectasis, which required a bronchoscopy; otherwise, no major complications were observed. The authors concluded that these early results indicated that anterior VBT is a safe and potentially effective treatment option for skeletally immature patients with idiopathic scoliosis. These patients experienced an improvement of their scoliosis with minimal major complications. However, longer term follow-up of this cohort will reveal the true benefits of this promising technique. (Level of Evidence: IV).

Furthermore, an UpToDate review on “Adolescent idiopathic scoliosis: Management and prognosis” (Scherl, 2017) does not mention anterior vertebral body tethering as a therapeutic option.

Magnetically Controlled Growing Rods:

In a prospective case-series study, Cheung et al (2012) evaluated the safety and effectiveness of a new magnetically controlled growing rod (MCGR) for non-invasive outpatient distractions in skeletally immature children with scoliosis. These investigators implanted the MCGR in 5 patients, 2 of whom have now reached 24 months' follow-up. Each patient underwent monthly outpatient distractions. These researchers used radiography to measure the magnitude of the spinal curvature, rod distraction length, and spinal length. They assessed clinical outcome by measuring the degree of pain, function, mental health, satisfaction with treatment, and procedure-related complications. In the 2 patients with 24 months' follow-up, the mean degree of scoliosis, measured by Cobb angle, was 67° (SD 10°) before implantation and 29° (4°) at 24 months. Length of the instrumented segment of the spine increased by a mean of 1.9 mm (0.4 mm) with each distraction. Mean predicted versus actual rod distraction lengths were 2.3 mm (1.2 mm) versus 1.4 mm (0.7 mm) for patient 1, and 2.0 mm (0.2 mm) and 2.1 mm (0.7 mm) versus 1.9 mm (0.6 mm) and 1.7 mm (0.8 mm) for patient 2's right and left rods, respectively. Throughout follow-up, both patients had no pain, had good functional outcome, and were satisfied with the procedure. No MCGR-related complications were noted. The authors concluded that the MCGR procedure can be safely and effectively used in outpatient settings, and minimizes surgical scarring and psychological distress, improves quality of life, and is more cost-effective than is the traditional growing rod procedure. The technique could be used for non-invasive correction of abnormalities in other disorders. The main drawbacks of this study were its small sample size and incomplete follow-up. Furthermore, the MCGR procedure was associated with increased radiation exposure from frequent radiographs. The authors noted

that a prospective, large-scale, multi-center trial is underway to further validate these preliminary findings and evaluate other aspects of this technology.

In a prospective, non-randomized study, Akbarnia et al (2013) reported the preliminary results of MCGR technique in children with progressive early onset scoliosis (EOS). Distractions were performed in clinic without anesthesia/analgesics. T1-T12 and T1-S1 heights and the distraction distance inside the actuator were measured after lengthening. A total of 14 patients (7 females) with a mean age of 8 yrs + 10 mos (3 yrs + 6 mos to 12 yrs + 7 mos) had 14 index surgeries, single rod (SR) in 5 and dual rod (DR) in 9, with overall 68 distractions. Diagnoses were idiopathic (n = 5), neuromuscular (n = 4), congenital (n = 2), syndromic (n = 2) and NF (n = 1). Mean follow-up was 10 mos (5.8 to 18.2). Cobb angle changed from 60° to 34° after initial surgery and 31° at latest follow-up. During distraction period, T1-T12 height increased by 7.6 mm for SR (1.09 mm/mo) and 12.12 mm for DR (1.97 mm/mo). T1-S1 height gain was 9.1 mm for SR (1.27 mm/mo) and 20.3 mm for DR (3.09 mm/mo). Complications included superficial infection in 1 SR, prominent implant in 1 DR and minimal loss of initial distraction in 3 SR after index. Partial distraction loss observed following 14 of the 68 distractions (1 DR and 13 SR) but regained in subsequent distractions. There was no neurologic deficit or implant failure. The authors concluded that these preliminary results indicated MCGR was safe and provided adequate distraction similar to standard growing rod. Dual rod achieved better initial curve correction and greater spinal height during distraction compared to single rod.

The MAGEC System is composed of an implantable rod, an external remote controller (ERC), and accessories. The implanted spinal rod is used to brace the spine during growth to minimize the progression of scoliosis. Magnetic components in both the MAGEC rod and

MAGEC ERC allow for distraction of the rod to be performed non-invasively and without the need for repeated surgeries as found in traditional growing rod systems. **http://ellipse-tech.com/magec-patients/ (http://ellipse-tech.com/magec-patients/)**.

Dannawi et al (2013) stated that conventional growing rods are the most commonly used distraction-based devices in the treatment of progressive early-onset scoliosis. This technique requires repeated lengthening with the patient anesthetized in the operating theatre. These investigators described the outcomes and complications of using a non-invasive magnetically controlled growing rod (MCGR) in children with early-onset scoliosis. Lengthening was performed on an out-patient basis using an external remote control with the patient awake. Between November 2009 and March 2011, a total of 34 children with a mean age of 8 years (5 to 12) underwent treatment. The mean length of follow-up was 15 months (12 to 18). In total, 22 children were treated with dual rod constructs and 12 with a single rod. The mean number of distractions per patient was 4.8 (3 to 6). The mean pre-operative Cobb angle was 69° (46° to 108°); this was corrected to a mean 47° (28° to 91°) post-operatively. The mean Cobb angle at final review was 41° (27° to 86°). The mean pre-operative distance from T1 to S1 was 304 mm (243 to 380) and increased to 335 mm (253 to 400) in the immediate post-operative period. At final review the mean distance from T1 to S1 had increased to 348 mm (260 to 420). Two patients developed a superficial wound infection and a further 2 patients in the single rod group developed a loss of distraction. In the dual rod group, 1 patient had pull-out of a hook and 1 developed prominent metal-work. Two patients had a rod breakage -- 1 patient in the single rod group and 1 patient in the dual rod group. The authors concluded that these results showed that the MCGR is safe and

effective in the treatment of progressive early-onset scoliosis with the avoidance of repeated surgical lengthening.

Hickey et al (2014) reported the early experience of a magnetically controlled growing rod system (MAGEC, Ellipse). These investigators performed a review of pre-operative, post-operative and follow-up Cobb angles and spinal growth in case series of 8 patients with a minimum 23 months' follow-up (23 to 36 months). A total of 6 patients had dual rod constructs implanted and 2 patients received single-rod constructs. Four patients had MAGEC rods as a primary procedure; 4 were revisions from other systems. Mean age at surgery in the primary group was 4.5 years (range of 3.9 to 6.9). In patients who had MAGEC as a primary procedure, mean pre-operative Cobb angle was 74° (63 to 94), with post-operative Cobb angle of 42° (32 to 56) $p \leq 0.001$ (43 % correction). Mean Cobb angle at follow-up was 42° (35 to 50). Spinal growth rate was 6 mm/year. One sustained proximal screw pull out. A final patient sustained a rod fracture. Mean age at surgery in the revision group was 10.9 years (range of 9 to 12.6). Mean pre-operative Cobb angle was 45° (34 to 69). Post-operative Cobb angle was 42° (33 to 63) (2 % correction). Mean Cobb angle at follow-up was 44° (28 to 67). Mean spinal growth rate was 12 mm/year. Two patients developed loss of distraction. The authors concluded that the MAGEC growing rod system effectively controlled early onset scoliosis when used as either a primary or revision procedure. They stated that although implant-related complications are not uncommon, the avoidance of multiple surgeries following implantation is beneficial compared with traditional growing rod systems.

Jenks et al (2014) noted that the MAGEC system comprises a magnetically distractible spinal rod implant and an external remote controller, which lengthens the

rod; this system avoids repeated surgical lengthening. Rod implants brace the spine internally and are lengthened as the child grows, preventing worsening of scoliosis and delaying the need for spinal fusion. The Medical Technologies Advisory Committee at the National Institute for Health and Care Excellence (NICE) selected the MAGEC system for evaluation in a NICE medical technologies guidance. A total of 6 studies were identified by the sponsor (Ellipse Technologies Inc.) as being relevant to the decision problem. Meta-analysis was used to compare the clinical evidence results with those of one conventional growth rod study, and equal efficacy of the 2 devices was concluded. The key weakness was selection of a single comparator study. The External Assessment Centre (EAC) identified 16 conventional growth rod studies and undertook meta-analyses of relevant outcomes. Its critique highlighted limitations around study heterogeneity and variations in baseline characteristics and follow-up duration, precluding the ability to draw firm conclusions. The sponsor constructed a de-novo costing model showing that MAGEC rods generated cost savings of £9,946 per patient after 6 years, compared with conventional rods. The EAC critiqued and updated the model structure and inputs, calculating robust cost savings of £12,077 per patient with MAGEC rods compared with conventional rods over 6 years. The year of valuation was 2012. NICE issued a positive recommendation as supported by the evidence (Medical Technologies Guidance 18).

The British National Health Service's draft policy on "Non-Invasively Lengthened Spinal Rods for Scoliosis" (NHS, 2014) provided the following selection criteria for the use of the MAGEC System:

- Spinal surgeon feels that an instrumented spinal fusion will result in an unacceptable reduction in final height and respiratory function, and

- Member is between the ages of 2 and 11 for girls and 2 and 13 for boys. Some children are not as skeletally mature as their chronological age so a radiograph confirming bone age within the acceptable age limits is satisfactory. Use outside the specified chronological and skeletal age range may be appropriate if the patient is particularly small for age, has late development or has an increase in respiratory risk.

The NHS also noted the following exclusion criteria regarding the use of the MAGEC system:

- Infection or pathologic conditions of bone such as osteopenia which would impair the ability to securely fix the device
- Metal allergies and sensitivities
- Person with pacemaker
- Person requiring MRI imaging during the expected period device will be implanted
- Person younger than 2 years old
- Person weighting less than 25 lb (11.4 kg).

Figueiredo et al (2016) examined the safety and effectiveness of MCGR for the treatment of pediatric scoliosis. This is an evidence-based systematic review of literature for the surgical management of patients with pediatric scoliosis using MCGR technique. A total of 6 clinical studies regarding the use of MCGR were included in this review, with a total of 68 patients, and mean age of 8.38 years. The dual-rod (DR) technique of rod construct with MCGR was used in 33.85 % and the single-rod (SR) in 66.15 % of the patients. The mean pre-operative main coronal curve for the DR was 65.9°, and for the SR was 69.6° ($p > 0.05$). At the latest follow-up, it was 36.8° for DR and 43.0 degrees for SR ($p < 0.05$). The mean pre-operative T1 - S1 spinal length was 298.7 mm for the DR and 303.5 mm for the SR group ($p < 0.05$). According to the latest follow-up, using the DR

construct, the spinal length increased to 347 mm with 13.92 % of total lengthening; and using the SR construct, the average lengthening was 339 mm, with 10.48 % of total lengthening ($p < 0.05$). Post-operative complications were similar, 25 % in DR and 31.57 % in the SR group ($p > 0.05$). The authors concluded that level IV of medical evidence supports the use of MCGR as a safe and effective alternative for the treatment of severe pediatric scoliosis. They stated that recommendation Grade C supports the role of MCGR with DR construct as an option to achieve a better correction of the scoliotic curve and to maximize the post-operative T1 - S1 spinal length.

In a prospective, non-randomized, radiological study, Thompson et al (2016) evaluated the preliminary results of using the MAGEC System to treat children with EOS. Between January 2011 and January 2015, a total of 19 children were treated with MCGRs and underwent distraction at 3-monthly intervals. The mean age of this study cohort was 9.1 years (4 to 14) and the mean follow-up 22.4 months (5.1 to 35.2). Of the 19 children, 8 underwent conversion from traditional growing rods. Whole spine radiographs were carried out pre- and post-operatively: image intensification was used during each lengthening in the out-patient department. The measurements evaluated were Cobb angle, thoracic kyphosis, proximal junctional kyphosis and spinal growth from T1 to S1. The mean pre-, post-operative and latest follow-up Cobb angles were 62° (37.4 to 95.8), 45.1° (16.6 to 96.2) and 43.2° (11.9 to 90.5), respectively ($p < 0.05$). The mean pre-, post-operative and latest follow-up T1-S1 lengths were 288.1 mm (223.2 to 351.7), 298.8 mm (251 to 355.7) and 331.1 mm (275 to 391.9), respectively ($p < 0.05$). In all, 3 patients developed proximal pull-out of their fixation and required revision surgery: there were no subsequent complications. There were no complications of out-patient distraction. The authors concluded that the findings of this study

showed that MCGRs provided stable correction of the deformity in EOS in both primary and revision procedures. They have the potential to reduce the need for multiple operations and thereby minimize the potential complications associated with traditional growing rod systems.

In a prospective, non-randomized study, Heydar et al (2016) evaluated the safety, effectivity profile of MCGR in patients with EOS. A total of 18 patients with progressive EOS were treated by MCGR, 2 of them had undergone final fusion operation. Patients were followed-up for a minimum time of 9 months from the time of initial surgery. Radiological data were analyzed in terms of Cobb angle, kyphosis angle, T1-T12 and T1-S1 distances in pre-operative, post-operative and last follow up. The mean pre-operative Cobb and kyphosis angle were 68° (44 to 116°), 43° (98 to 24°), it was corrected to 35° (67 to 12°), 29° (47 to 21°) immediately after initial operation and maintained at 34.5° (52 to 10°), 33° (52 to 20°) at last follow up, respectively. The mean pre-operative T1-T12 and T1-S1 distance were 171 mm (202 to 130), 289 mm (229 to 370), it was increased to 197 mm (158 to 245), 330 mm (258 to 406) immediately after initial operation and further increased to 215 mm (170 to 260), 35 7mm (277 to 430) at last follow-up, respectively; 2 patients had undergone final fusion, they had overall mean Cobb angle correction of 66° (62 to 70), kyphosis angle change of 53° (26 to 80). Total height gain in T1-T12 and T1-S1 of 80.5 mm (67 to 94) and 119 mm (105 to 133), respectively. The authors concluded that MCGR is safe and effective technique in correction of EOS deformity and in maintaining the correction during non-surgical distraction procedures. A further correction of the deformity and more spinal height gain can be achieved in the final fusion operation.

Ridderbusch et al (2015) stated that growth-sparing techniques for the treatment of EOS have developed significantly over the last years. Traditional growing rods (GRs) require repeated surgical lengthening under anesthesia. Since June 2011 these researchers have been using the MCGR to treat patients with progressive EOS. A total of 35 patients with EOS of different etiologies underwent treatment with MCGR. These researchers recorded about the preliminary results of 24 patients who fulfilled the inclusion criteria of a minimum follow-up (FU) of 12 month and greater than 3 lengthening. The mean age at surgery was 8.9 ± 2.5 years. Correction of the primary curve after the index surgery and after lengthening was measured on standing radiographs using the Cobb technique; T1-T12 and T1-S1 spinal length were also measured. Intra-operative and post-operative complications were recorded. The mean FU was 21.1 ± 7.3 months. All patients had a minimum of 3 out-patient lengthening [mean of 4.6 ± 1.5 (range of 3 to 8)]. The mean primary curve was 63 ± 15 degrees (range of 40 to 96) and improved to 29 ± 11 degrees (range of 11 to 53; $p < 0.001$) after MCGR. The mean major curve after most recent lengthening was 26 degrees (range of 8 to 60; $p < 0.07$). The T1-T12 as well as the T1-S1 length increased significantly ($p < 0.001$). The mean pre-operative thoracic kyphosis decreased from 43 ± 24 degrees (range of -32 to 86) to 27 ± 12 degrees (range of 9 to 50 degrees; $p < 0.001$) after surgery, respectively, and measured 32 ± 12 degrees (range of 12 to 64; $p < 0.05$) at last FU. In 1 patient a loss of distraction occurred making rod exchange necessary; 3 patients developed a proximal junctional kyphosis and in another patient a screw pull out occurred that required revision surgery. The authors concluded that these findings demonstrated that MCGR is a safe and effective non-fusion technique in the treatment of progressive EOS avoiding repeated surgical lengthening procedures. It provided adequate distraction similar to standard GR.

The magnetically induced transcutaneous lengthening allows non-invasive distraction achieving spinal growth comparable to conventional GR techniques.

La Rosa et al (2017) presented a series of 10 patients with early-onset scoliosis (EOS) managed with magnetically controlled growing rod (MCGR) (Ellipse TM MAGEC System, Irvine, CA). These investigators implanted MCGR in 10 patients affected by EOS. Scoliosis and kyphosis angles, T1-T12 and T1-S1 length were evaluated pre-operatively, post-operatively, and at the last follow-up. A visual analog scale (VAS) score was used to evaluate pain during out-patient rod distraction procedures. The mean follow-up was 27 months. All patients attended distractions of the magnetic rod through an external remote control every 3 months. The mean predicted distraction was 3 mm at each lengthening session. The mean Cobb angle value was 64.7 ± 17.4 degrees (range of 45 to 100) pre-operatively and 28.5 ± 13.9 degrees (range of 15 to 59) at the latest follow-up. The mean T1-S1 length value was 27.1 ± 5.4 cm (range of 16 to 34.8 cm) pre-operatively and 32.8 ± 4 cm (range of 26.5 to 39) at the latest follow-up. The mean T1-T12 length value was 16.2 ± 2.7 cm (range of 10 to 19 cm) pre-operatively and 20.6 ± 2.9 cm (range of 15.5 to 23.5 cm) at the latest follow-up. The average monthly T1-T12 height increase was 0.8 mm, whereas the average monthly T1-S1 increase was 0.9 mm; 2 patients experienced a rod breakage and 1 patient had a pull-out of the apical hooks. The authors concluded that although implant-related complications could occur, as in all EOS growing rods procedures, MCGR can be effectively used in patients with EOS. This spinal instrumentation can overcome many of the complications related with the traditional growing rods implants. This procedure can be effectively used in out-patient settings, minimizing surgical scarring, surgical

site infection, and psychological distress due to multiple surgeries needed in the traditional growing rods system, improving quality of life, and saving health care costs.

Estrogen Receptor Beta (ESR2) Rs1256120 Single Nucleotide Polymorphism Testing:

In a systematic review and meta-analysis, Zhao and colleagues (2016) evaluated the current evidence on the association between rs1256120 single nucleotide polymorphism (SNP) of the estrogen receptor beta gene (ESR2) and AIS. Using a sensitive search strategy, PubMed (Medline), Embase, and HuGE Literature Finder databases were searched to identify relevant studies for inclusion in the systematic review and meta-analysis. Risk of bias was assessed using a modified Newcastle-Ottawa Scale. The inverse variance model was used to calculate summary ORs and corresponding 95 % CIs for the allelic (C versus T) and genotypic comparisons. Planned subgroup and sensitivity analyses were performed. A total of 3 studies were included for systematic review and meta-analysis (n = 1,264 AIS cases and n = 1,020 controls). A null relationship was found between rs1256120 and AIS (allelic OR = 1.20, 95 % CI: 0.81 to 1.78, p = 0.36, I = 84.9 %), with the first reported association likely to be false-positive and contributing substantially to heterogeneity. The authors concluded that findings from the systematic review and meta-analysis suggested that rs1256120 of ESR2 is unlikely to be a predisposing or disease-modifying genetic risk factor for AIS.

IGF1 Gene Rs5742612 Single Nucleotide Polymorphism Testing:

In a meta-analysis, Guan and colleagues (2016) evaluated the association between insulin-like growth factor 1 (IGF1) gene SNP (rs5742612) and AIS. These investigators searched PubMed, Embase, Web of

Science and Cochrane Library up to January 19, 2016 to obtain relevant studies using our research strategy. A total of 4 articles all belonging to case-control studies were included in this meta-analysis. The 4 studies contained 763 cases and 559 controls who satisfied the inclusion criteria after judgment by 2 reviewers. No significant associations were detected between IGF1 gene SNP (rs5742612) and AIS (T versus C, OR = 1.10, 95 % CI: 0.91 to 1.34, p = 0.32; TT versus CC: OR = 1.28, 95 % CI: 0.82 to 2.02, p = 0.28; TC versus CC: OR = 1.29, 95 % CI: 0.82 to 2.06, p = 0.27; TT/TC versus CC: OR = 1.28, 95 % CI: 0.83 to 1.98, p = 0.27; TT versus TC/CC: OR = 1.06, 95 % CI: 0.82 to 1.36, p = 0.66). The authors concluded that IGF1 gene SNP (rs5742612) is not significant associated with susceptibility to AIS in either Asian or Caucasian populations. However, IGF1 gene rs5742612 may be associated with severity of AIS. They stated that further studies with larger sample size and different population groups involving the relationship are needed to confirm the potential association.

Manual Therapy:

Czaprowski (2016) evaluated the effectiveness of non-specific manual therapy (NMT; including manual therapy, chiropractic, osteopathy) used in the treatment of children and adolescents with IS. The study analyzed systematic reviews (Analysis 1) and other recent scientific publications (Analysis 2). Analysis 1 encompassed papers on the use of NMT in patients with IS. Works concerning specific physiotherapy (SP) or bracing (B) and other types of scoliosis were excluded from the analysis. Inclusion criteria for Analysis 2 were: treatment with NMT; subjects aged 10 to 18 years with IS. The following types of papers were excluded: works analyzing NMT combined with SP or B, reports concerning adult patients, analyses of single cases and publications included in Analysis 1. Analysis 1: a total of 6 systematic reviews contained 6 papers on the

effectiveness of NMT in the treatment of IS. The results of these studies were contradictory, ranging from Cobb angle reduction to no treatment effects whatsoever. The papers analyzed are characterized by poor methodological quality: small group sizes, incomplete descriptions of the study groups, no follow-up and no control groups. Analysis 2: a total of 217 papers were found; none of them met the criteria set for the analysis. The authors concluded that (i) few papers verifying the effectiveness of manual therapy, chiropractic and osteopathy in the treatment of IS have been published to date, (ii) the majority were experimental studies with poor methodology or observational case studies, (iii) the effectiveness of NMT in the treatment of patients with IS cannot be reliably evaluated, and (iv) it is necessary to conduct further research based on appropriate methods (prospective RCTs) in order to reliably evaluate the usefulness of NMT in the treatment of IS.

CPT Codes / HCPCS Codes / ICD-10 Codes	
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":	
CPT codes covered if selection criteria are met:	
+20930	Allograft, morselized, or replacement of osteopromotive material, for spine surgery only
+20937	Autograft for spine surgery only (includes harvesting the graft); morselized (through separate skin or fascial incision)
22214	Osteotomy of spine, posterior or posterolateral approach, one vertebral segment; lumbar
+22216	each additional vertebral segment
22548 - 22819	Arthrodesis

+22840	Posterior non-segmental instrumentation (e.g., Harrington rod technique, pedicle fixation across one interspace, atlantoaxial transarticular screw fixation, sublaminar wiring at C1, facet screw fixation)
+22842	Posterior segmental instrumentation (e.g., pedicle fixation, dual rods with multiple hooks and sublaminar wires); 3 to 6 vertebral segments
+22843	7 to 12 vertebral segments
+22844	13 or more vertebral segments
+22845	Anterior instrumentation; 2 to 3 vertebral segments
+22846	4 to 7 vertebral segments
+22847	8 or more vertebral segments
+22848	Pelvic fixation (attachment of caudal end of instrumentation to pelvic Bony structures) other than sacrum
22849	Reinsertion of spinal fixation device
22852	Removal of posterior segmental instrumentation
29010	Application of Risser jacket, localizer; body only
97014	Application of a modality to one or more areas; electrical stimulation (unattended)
97032	Application of a modality to one or more areas; electrical stimulation (manual), each 15 minutes
CPT codes not covered for indications listed in the CPB:	
***Melatonin receptor 1B gene (MTNR1B) rs4753426 and rs10830963 polymorphism testing, estrogen receptor beta (ESR2) rs1256120 and insulin-like growth factor 1 (IGF1) gene rs5742612 single nucleotide polymorphism testing* - no specific code**:	

22505	Manipulation of spine requiring anesthesia, any region [not covered for adult scoliosis]
27280	Arthrodesis, open, sacroiliac joint, including obtaining bone graft, including instrumentation, when performed
98925 - 98929	Osteopathic manipulation (OMT)
98940 - 98943	Chiropractic manipulative treatment (CMT) [not covered for adult scoliosis]
Other CPT codes related to the CPB:	
77072	Bone age studies
HCPCS codes covered if selection criteria are met:	
***MAGEC System* - no specific code**:	
L1000 - L1499	Orthotic devices - scoliosis procedures
HCPCS codes not covered for indications listed in the CPB:	
E0744	Neuromuscular stimulator for scoliosis
ICD-10 codes covered if selection criteria are met:	
M41.00 - M41.08	Infantile idiopathic scoliosis
M41.112 - M41.27	Juvenile, adolescent and other idiopathic scoliosis
Vertebral body tethering:	
No specific code	

The above policy is based on the following references:

Electrical Stimulation:

1. Moe JH, Kettelson DN. Idiopathic scoliosis: Analysis of curve patterns and the preliminary results of Milwaukee brace treatment in one

hundred sixty-nine patients. J Bone Joint Surg. 1970;52(8):1509-1533

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